(c) SEQ ID NO: 98;

(d) SEQ ID NO: 26;

(e) SEQ ID NO: 27;

(f) SEQ ID NO: 28;

(g) SEQ ID NO: 99; and

(h) glycine-serine-proline.

I 8 Cont

REMARKS

Status of the Claims

Claims 124 and 132-164 are pending in the application. Claims 54-123, 125-131, 138, 144, 154, 161 and 162 have been canceled, without prejudice. Claims 124, 132-137, 139-143, 145-149 and 155-159 have been amended in order to more particularly point out and distinctly claim that which Applicants regard as the invention. New Claims 165-173 are presented. Support for the amended claims and new claims can be found generally throughout Applicants' Specification.

The Specification Fully Enables the Claimed Invention

In the parent of the present application U.S. Serial number 08/485,943, the Examiner rejected Claims 124 and 132-164 under 35 U.S.C. §112, first paragraph, suggesting that "the specification, while being enabling for the use of a gene encoding the OB polypeptide as shown in SEQ ID NOS: 2, 4, 5 or 6 as well as any OB polypeptide thereof lacking the signal sequence of amino acids 1-21, for modulating the body weight of *ob/ob* mice or normal mice, does not reasonably provide enablement for using other variants (except natural alleles), muteins, analogs and fragments of these OB polypeptides, nor is the specification enabling for modulating the body weight of any other mammals, including humans". The Examiner presented two specific issues regarding enablement of the scope of the claims. These issues are addressed by the Applicants, below. Applicants request that the Examiner enter above amendments in the instant application and consider the comments presented prior to issuance of a first substantive office

action in the instant application.

1. Variants, Analogs or Fragments of the OB Polypeptide are Enabled in the Claims as Amended.

In the first issue, the Examiner asserted that the Specification failed to enable other variants, analogs or fragments of the OB polypeptide to function as claimed. Applicants respectfully disagree and submit that the Specification provides sufficient guidance and a significant and representative number of such variants, analogs and fragments, including modifications at any of 22 divergent sites between mouse and human OB polypeptide, capable of modulating body weight to enable the full scope of the claimed genus of sequences encoding OB polypeptide. Applicants note that the Examiner made particular comments in his response, at page 4, which are relevant:

> ... applicant has clearly indicated that these 22 cites [sic, sites] were clearly demonstrable of species differences in the OB protein which ***do not*** affect the characteristics of the OB protein in its ability to affect weight in an *ob/ob* mouse. The skilled artisan could easily be directed to make specific amino acid changes within any or all of these specific sites and reasonably expect to obtain an protein which would be identifiable both structurally and functionally as an OB protein. In fact, it could be argued that applicant has set forth a comparison of the mouse and human genes and identified the specific sites where specific amino acids may differ, thus demonstrating a "generic mammalian OB protein" which is constant over the 83% of the amino acids found at specific sites. The other remaining sites could vary without affecting the identity of the OB protein.

In an effort to facilitate prosecution, and without prejudice to continued prosecution, the claims presented herein all are particularly directed to use of a gene encoding the OB polypeptide as shown in SEQ ID NOS: 2, 4, 5 or 6, any OB polypeptide thereof lacking the signal sequence of amino acids 1-21, and to particular variants and analogs which incorporate modifications at the 22 divergent sites, all of which are explicitly supported and enabled by the Specification.

In light of the above comments, the Examiner's rejection regarding the lack of enablement of variants, analogs or fragments of the OB polypeptide to function as claimed should be withdrawn.

2. Enablement for the Methods which Modify the Body Weight of a Mammal.

The Examiner's second contention is in regard to the scope of enablement for the methods which modify the body weight of a mammal. The Examiner, in an earlier rejection (Paper No. 17 dated May 21, 1998), using treatment of humans as an example, noted that because the Specification fails to identify the individuals within a population of obese humans who would benefit from administration of a vector encoding the OB protein, the invention cannot be said to be enabled for modulating body weight as broadly claimed. However, the Examiner further stated, at pages 11-12, that:

> It is clear from the teachings of the Muzzin *et al.* reference, cited in the previous office action, that administration of a vector containing the leptin protein will cause a "total correction of the obese phenotype of the *ob/ob* mice." It is also evident from the teachings of Campfield *et al.*, also cited in the previous office action, that not all obese mice will respond to such treatments because the defect causing the obesity lies in a gene other than the [sic] that encoding the OB protein.

The Examiner further refers to previously cited references which he indicated as teaching that obesity in humans, in particular, is a complex issue, including Sorensen *et al.* 1995 and Maffei 1996. The Examiner also stated at pages 12-13 of his earlier rejection:

> Given the lack of guidance of the specification on how to affect body changes in humans, the uncertainty in the state of the art as to the complex causes of obesity in humans, the unpredictability of gene therapeutics in general in the art and the lack of any current art recognized genetic alterations of body weight in humans, it would require undue experimentation to practice the invention for its scope.

Guidance Found in the Specification

The claims of the present invention are directed to modifying body weight in mammals, including, for example, humans and mice. While Applicants do not deny that the cited references indicate that obesity in humans can be due to defects other than in the *OB* gene or its encoded polypeptide, Applicants respectfully take issue with the Examiner's contention that it would constitute undue experimentation to identify the individuals within a population of obese

humans who would benefit from administration of a vector encoding the OB protein.

Identification of those Individuals Who May Benefit from Treatment

First, the teachings of the Specification provide significant guidance for the skilled artisan to make and use the present invention and the publications cited by the Examiner confirm that this guidance was sufficient for those of skill in the art to make and use the claimed methods of the present invention. The instant Application describes the discovery of the *OB* gene and its encoded polypeptide in mice and humans (as well as identification of homologous sequences in other mammals, including rats, rabbits, sheep, cows, pigs and chickens). This discovery has provided the answer to a long sought question of identification of "an art recognized genetic alteration of body weight". See Marx, Science 266:1477-78 (1994).

While not all obesity in humans is necessarily related to alterations in the *OB* gene or its encoded peptide, Applicants submit that those of skill in the art have recognized that the *OB* gene and its encoded peptide play a significant role in obesity. For example, Sorensen *et al.*, cited by the Examiner, states that "a number of genes have been positively associated with BMI and obesity in ***both humans and animal models***" (***emphasis added***), among them the mouse *ob* gene and its human homolog (page 5, column 2, 3rd paragraph). Given that the present Specification describes how to identify the *OB* gene, isolate the *OB* gene, express its protein product and analyze the effects of the protein, be it wild-type or mutated, those of skill in the art would readily be able to determine whether aberration in the particular gene is responsible for obesity in a given human or other mammalian subject, without undue experimentation.

The skilled artisan can, using diagnostic methods known in the art and provided by the teachings of the Specification, *e.g.*, at pages 65-69, identify those individuals, including those with altered or unaltered levels or forms of OB polypeptide, which could reasonably be expected to benefit from the administration of the *OB* gene (or polypeptide) to modify body weight as claimed. Using standard methods and methods described in the Specification, the skilled artisans of Maffei *et al.*, as cited by the Examiner, were able to test without undue experimentation individuals within a population of obese humans to determine whether such individuals had an alteration in the coding region of the *OB* gene. In light of this teaching, Applicants are puzzled by the Examiner's position that it would take undue experimentation to identify such individuals.

On the other hand, Applicants demonstrated that *db/db* mice have increased levels of OB mRNA and do not respond to administration of OB polypeptide (see, *e.g.*, Specification at page 98 and in Example 8, as detailed on page 114, lines 24-26). As cited by the Examiner, Campfield *et al* hypothesized that the administration of recombinant OB protein to *db/db* obese mice did not reduce food intake and body weight because "the genetic defect in *db/db* mice renders them unable to appropriately respond to OB protein, perhaps because of a defect in the OB protein receptor or the postreceptor signaling pathway." This hypothesis was subsequently proven true, with the *db* gene now identified as encoding the OB polypeptide receptor. Armed with this information, the skilled artisan, using methods similar to those diagnostic methods outlined above for the OB polypeptide, can readily identify those individuals with altered or unaltered levels or forms of DB polypeptide.

Furthermore, Applicants respectfully submit that the law does not require that the Specification enable the treatment of ***every*** obese patient, the law merely requires objective enablement in which the methods are shown to be effective in at least some individuals in the population being examined. Although the Maffei *et al.* study may indicate that mutations in the *OB* gene coding region are not common, the authors did not rule out the possibility of sequence variation in noncoding regions of the *OB* gene which may be important for the quantitative expression of OB protein (*Diabetes*, 45:679-82 (1996) at 681).

How to Modulate Body Weight in Mammals, Including Humans

Although applicants acknowledge that environment plays a role in obesity, its role is conditional on a given genetic background. This genetic background, and the susceptibility of a particular genetic background to OB gene therapy methods, is readily evaluated by the skilled artisan without undue experimentation using the methods disclosed in the present Specification. The present invention particularly contemplates gene therapy to control or reduce obesity in a patient (see the Specification at page 8, lines 1-7). The Specification at pages 72-85 further discloses therapeutic applications of the compositions of the present invention including nucleic acid-based treatments. The Specification at page 83, line 16 through page 85, line 10 specifically contemplates that gene therapy into ***human*** cells would be expected to decrease body weight. This section provides exemplary methods of introducing the gene *in vivo* using, for example,

various viral vectors including adenoviruses, retroviruses, adeno-associated viruses as well as many others. Given this disclosure, one of ordinary skill in the art would merely follow the directions in the specification to identify obese individuals who "would benefit from administration of a vector encoding the OB protein."

As stated above, the Examiner has admitted (Paper No. 27 mailed 4/6/99) that the specification is enabling for the use of a gene encoding certain OB polypeptides (as discussed above) "for modulating the body weight of *ob/ob* mice or normal mice." This disclosure is sufficient to enable methods for modulating the body weight of any other mammal, including humans. The MPEP clearly states that an "*in vivo* animal model example in the specification, in effect, constitutes a 'working example' if . . . [the] particular model is recognized as correlating to a specific condition . . . unless the Examiner has evidence that the model does not correlate" MPEP 2164.02. Furthermore, the MPEP goes on to state that even if there is evidence that an animal model is not an exact match for the human condition, such evidence for and against correlation must be weighed to decide whether one skilled in the art would accept the model as reasonably correlating to the condition in humans. *Id.* citing *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

Data obtained from animal studies has long been recognized to be indicative of human utility. *In re Hartrop*, 135 U.S.P.Q. 419 (CCPA 1962). At this point it is beyond doubt that data from mice are predictive of utility in humans. See *In re Bergel and Stock*, 130 U.S.P.Q. 206, 209 (CCPA 1961); *In re Ross and Davis*, 134 U.S.P.Q. 321 (CCPA 1962), citing *Bergel*; *Ex parte Westphal* and *Damagk*, 139 U.S.P.Q. 378 (POBA 1962). Furthermore, even if the Examiner maintains the stance that environmental conditions play a larger role in human obesity than animal model obesity, Applicants refer the Examiner to MPEP 2164.02 which instructs that "a rigorous or an invariable exact correlation is not required." As such, and as a matter of law, the animal model data provided by the Applicants is sufficient to enable the scope of the claims.

Human Clinical Trial Results Show Claimed Invention was Enabled

It has been demonstrated that recombinant human leptin therapy in a severely obese human subject having a leptin deficiency was effective in producing weight loss within two weeks of initiation of leptin therapy (Farooqi *et al.*, *New Engl. Jour. Med.*, 341(12):879-884

(1999)). These data, which independently confirm the data presented and predicted in the present application, were haled by Farooqi *et al.*, as confirming the importance of leptin in the regulation of body weight in humans (*Id.* at 883). In an additional randomized, controlled, dose escalation trial, it was shown that administration of recombinant human leptin produced a dose-responsive weight and fat loss in both lean and obese human adult subjects (Heymsfield *et al.*, *Jour. Am. Med. Assoc.*, 282 (16):1568-1575, 1999). Clearly, those of skill in the art have been able to duplicate and apply the methods and compositions initially contemplated in the present invention.

Leptin-Based Gene Therapy Successful in Animal Models

The Examiner acquiesces that gene therapy as contemplated by the Applicants' specification is effective to produce weight loss in obese mice and normal mice. As a matter of fact, the Examiner provides objective proof of this acquiescence by citing the results of independent studies published after the instant invention's priority date that confirm the inventors' findings. More particularly, Fletcher *et al.* (1995), Fletcher *et al.* (1996) and Muzzin *et al.* (1996) discuss studies demonstrating the efficacy of *OB* gene therapy *in vivo*.

In Fletcher *et al.* (1996), the authors reported the results of retroviral vector-mediated expression of soluble leptin in mice. Importantly, Fletcher *et al.* (1996) demonstrated the feasibility of *in vivo* gene therapy to modify body weight in both wild-type and obese (*ob/ob*) animals, finding that chronic expression of leptin resulted in reduction of body weight in both wild-type and obese animals. The earlier Fletcher *et al.* abstract (1995) reported the *ex vivo* manipulation of *ob/ob* bone marrow by transduction with wild-type *OB* cDNA and the subsequent transplantation into *ob/ob* animals resulting in significant weight loss. In conclusion, the authors stated that:

> these data demonstrate the feasibility of gene replacement therapy for the treatment of obesity and provide a basis for further investigations.

Similarly, Muzzin *et al* report correction of obesity and diabetes in genetically obese *ob/ob* mice by leptin gene therapy. Treatment of the *ob/ob* mouse with a recombinant adenovirus expressing the mouse leptin cDNA resulted in dramatic reductions in both food intake and body weight, as well as the normalization of serum insulin levels and glucose tolerance. In total, these references clearly confirm the feasibility of *OB* gene therapy methods to modify body

weight in mice, humans and other mammals, as taught by the Specification, and confirm that the gene therapy aspects of the present invention are enabled and can be practiced by the skilled artisan without undue experimentation. Thus, there is proof that leptin-based gene therapy is effective for modifying body weight in mammalian animals. Given that it has been demonstrated that the animal data presented in the specification regarding leptin administration correlated to human treatments (see *e.g.*, Farooqi *et al.*, 1999; Heymsfield *et al.*, 1999 discussed above), there is no reason to believe that the animal data pertaining to leptin-based gene therapy intervention will not correlate to human treatments.

Successful Application of Gene Therapeutics in General

Moreover, there are numerous reports that herald the general use of gene therapy for intervention in various diseases. In a recent review of clinical trials in various lung disorders, the authors state that "gene transfer has been safely achieved in patients with lung diseases . . . and . . . gene therapy will be an important tool for the 21st-century clinician." (Albelda *et al.*, *Ann Intern Med*, 132(8):649-60, 2000). The Recombinant DNA Advisory Committee of the National Institutes of Health (NIH) reported in March 1999 that 248 human gene therapy trials had been registered at the Office of Recombinant DNA Activities. (Romano *et al.*, *Stem Cells*, 18(1):19-39, 2000). Gene therapy has now successfully been employed to provide a full correction of the disease phenotype and provide clinical benefit against severe combined immunodeficiency X1 disease (Cavazzana-Calvo *et al.*, *Science*, 288:669-671, 2000). Gene therapy intervention contemplated for children with leukemia is being evaluated in clinical trials (Heslop, *Clin Lab Med*, 20(1):183-95, 2000). Clinical trials relating to gene therapy for the treatment of hemophilia A and B also are currently underway. At the recent Third Annual Meeting of the American Society of Gene Therapy , it was reported that a Phase I trial of AAV-mediated gene therapy for Hemophilia B showed changes in clinical endpoints including circulating levels of Factor IX and frequency of protein infusion (Manno *et al.*, *Mol. Ther.*, 1(5):S128, 2000).

These gene therapy regimens have had a sustained clinical effect in the subjects. Thus, there is unequivocal evidence that the scientific community accepts gene therapy as a practical approach to the therapeutic intervention of various disorders. This belief that gene therapy is viable for human treatment was prevalent even in the early 1990's where according to

one review "the most remarkable conclusion drawn from the human trials is that human gene therapy is indeed feasible...gene can be transferred to humans". (Crystal, *Science*, 270:404-405, 1995). Crystal went on to conclude that the evidence was overwhelming that human gene transfer had been demonstrated.

In the face of the wide-spread acceptance of gene therapy as a potential therapeutic regimen, the PTO's dogma that gene therapy is unpredictable and not viable is puzzling, and Applicants submit that, contrary to the Examiner's assertions regarding "the unpredictability in the art of gene therapy," gene therapy is a viable and widely applicable albeit young technology for use in the treatment of disease.

In addition to the scientific community's general acceptance of gene transfer protocols for therapeutic applications, the PTO itself has issued numerous patents directed to the gene therapy of various conditions including, for example, cystic fibrosis (U.S. Patent No. 5,240,846), cancer (U.S. Patent No. 6,051,218; U.S. Patent No. 6,017,896; U.S. Patent No. 5,922,685), muscular dystrophy (U.S. Patent No. 5,985,846), Gaucher disease (U.S. Patent No. 5,911,983), ocular disorders (U.S. Patent No. 5,827,702) and the like. Indeed, one patent is directed to gene therapy for treating obesity in mammals (U.S. Patent No. 6,001,816) which appears to be directed to the use of an adenoviral vector encoding a leptin gene delivered intravenously to a mammal with a deficiency in functional leptin to decrease weight.

Given the manifest weight of the evidence that gene therapy generally is a viable therapeutic technique and that the instant application provides particular guidance regarding leptin-encoding genes, Applicants assert that the instant invention is enabled for gene therapy intervention in modulating body weight and request a favorable consideration of the claims of the instant invention.

In view of the foregoing remarks, Applicants submit that the Examiner's rejection under 35 U.S.C. 112, first paragraph, may properly be withdrawn.

Particularity and Distinctiveness of the Claims

The Examiner in the previous application rejected Claims 133, 141, 147, 157 and 164 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention.

Regarding Claims 133, 141, 147 and 157, the Examiner comments that the Specification fails to set forth the meaning of the term " amino acid sequence identity" as claimed and how Applicant arrived at this identity. Applicants respectfully disagree. The skilled artisan will understand and can readily determine those amino acids which are identical, particularly in light of the teaching in the Specification. Clarification, meaning and support for the term "amino acid identity" is found in the comparison of the disclosed amino acid sequences of mouse and human OB polypeptides. Specifically the Specification characterizes the percentage (%) identity between the mouse and human OB amino acid sequences, where at page 12, lines 20-21, the Specification states that

> Overall, there is 83% identity at the amino acid level, ...

and at page 102, lines 15-17, the Specification states that

> Comparison of the human and mouse ob polypeptide sequences showed that the two molecules share an overall 83% identity at the amino acid level (Figure 4).

Figure 4, which provides a comparison of the mouse and human amino acid sequences aligned with one another, demonstrates that there are 28 amino acid differences between the human and mouse sequences, out of a total of 167 amino acids. Thus, 139 amino acids, or 83%, are identical, i.e. Alanine for Alanine, Glutamine for Glutamine. It is particularly straightforward for the skilled artisan to make such a comparison since the length of the mouse and human OB polypeptides are the same and the corresponding amino acids to compare in assessing identity is very readily determined - no gaps exist and no accounting for regions of extra amino acids is necessary. In addition, the skilled artisan's comparison of SEQ ID NO: 5 (which is the mouse variant OB polypeptide with glutamine 49 deleted) with SEQ ID NO:6 (which is the human variant OB polypeptide with glutamine 49 deleted) will yield the same result of 83% amino acid identity in a similarly straightforward fashion.

With regard to Claim 164, the Examiner asserts that the Specification fails to teach what is a "moderate stringency hybridization condition". Applicants respectfully disagree and point out that the Specification clearly teaches what is a moderate stringency hybridization condition, including at pages 44-45, where hybridization conditions are particularly discussed and specifically elaborated. Applicants further point out that Claim 164 also requires that any such hybridizing nucleic acid molecule have an important and specific additional functional

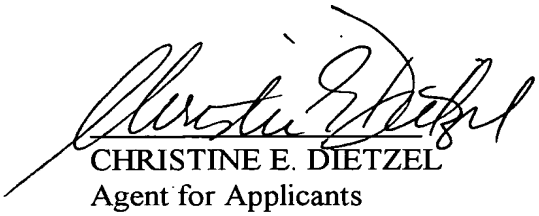
characteristic in that it must encode an OB polypeptide "capable of modulating body weight".

In view of the foregoing remarks, Applicants request that the Examiner's rejection under 35 U.S.C. 112, second paragraph, be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as presented herein are believed to be in condition for allowance, and early indication of such a favorable indication is respectfully requested. Should the Examiner feel that further issues remain upon a review of this preliminary amendment, he is invited to call the undersigned at the number listed below to effect their resolution.

Respectfully submitted,



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